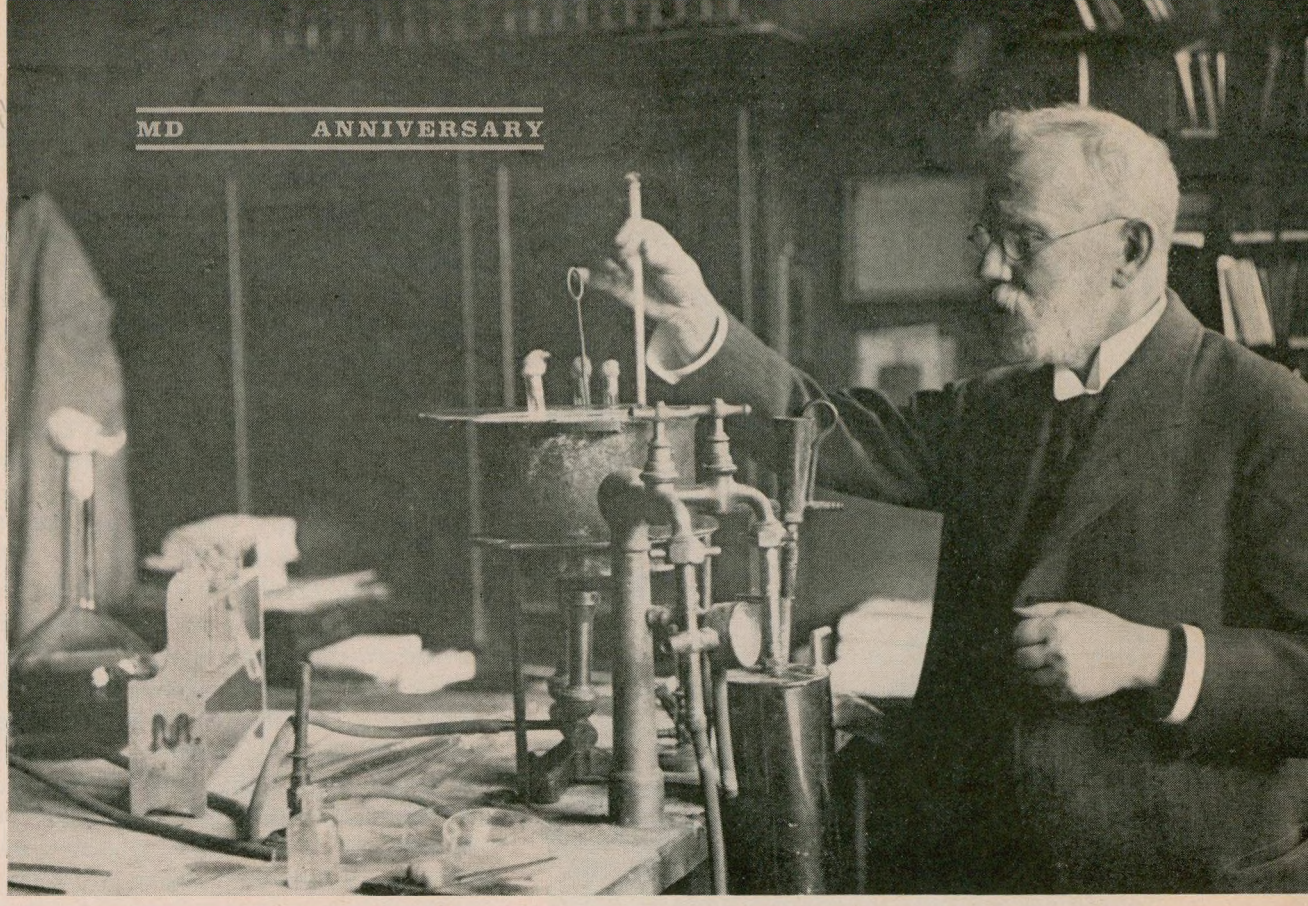


Dr. Paul Ehrlich, winner with Elié Metchnikoff of the 1908 Nobel Prize for Physiology and Medicine.

MAGIC MARKSMAN

On a spring day in 1876 the illustrious bacteriologist Robert Koch, visiting the laboratories in Breslau University, passed a shy, dye-bespattered student standing by a microscope and a pile of histology slides. Said the accompanying professor commiseratingly: "That is little Ehrlich. He is very good at staining but he will never pass his examinations."

Little Ehrlich not only passed his examinations, but later won the Nobel Prize for his work in immunology, fathered chemotherapy and gave to the world the first specific cure for syphilis.

Early Years. Born March 14, 1854, of prosperous Jewish parents in the town of Strehlen, Silesia, in southeastern Germany,* Paul Ehrlich had a happy childhood; the only boy in a houseful of girls he was adored by his family. His father, innkeeper and proprietor of the *Krug zum Rautenkranz* (tavern of the Wreath of Rue) was a jolly man with a few eccentricities: he sometimes sat at the window for hours talking to himself, jerking his head and waving his hands. When he told a joke he repeated it over and over, laughed loudly each time. From the elder Ehrlich, Paul seems to have copied the curiously jerky speech and agitated hand movements that remained lifelong idiosyncrasies.

The stabilizing force in the family and the tavern was Frau Ehrlich, a stout, energetic woman who brooked no nonsense from anyone.

At eight the boy concocted his own prescription for cough drops, had them made up by the local pharmacist. His idol was cousin Karl Weigert (later an eminent pathologist) nine years older. His avocation was to lead a troupe of boys as "brigands" in the hills around Strehlen.

When Ehrlich was about 14, Weigert taught him the technique of staining bacteria with aniline dyes, then the fashion in German chemistry. He experimented with them in a home laboratory while a lyceum student. In medical school, instead of the assigned laboratory exercises, he performed more tests with dyes.

*Now Strzelin, Poland.

Ehrlich's birthplace in Strehlen, Silesia, in southeastern Germany, now part of Poland. His father was the proprietor of the prosperous Wreath of Rue tavern.

Rare early photograph of Paul Ehrlich as a boy with one of his sisters. The only son in a houseful of daughters, the future physician was the idol of his family.

Ehrlich studied medicine at the universities of Breslau, Strasbourg and Leipzig. His slovenliness and individualistic habits plagued rigid professors, caused many to overlook his genius. Before he received his medical diploma in 1878 (aged 24) he had made the important discovery that connective tissue contains cells packed with large granules (mast cells) which have an affinity for basic organic dyes.

On graduation Ehrlich went to Berlin as an assistant to Dr. Friedrich Theodor von Frerichs, chief of the Charité hospital, who saw to it that the young physician's routine clinical work left him enough time for experiments.

Histology. Ehrlich's scientific work during this period was phenomenal and formed the basis for his future contributions to medicine: in nine years at the Charité he discovered that there were many types of leukocytes in the blood, distinguishable by staining dyes; he also discovered the diazo reaction of urine (named after him) in typhoid fever and the simple fuchsin method of staining the tubercle bacillus, two important diagnostic procedures still in use with little variation today.

The first to stain the tissues of living animals, Ehrlich found that when methylene blue was injected into the bloodstream, it colored only the central nervous system tissues and none other; it occurred to him then that chemicals might also be found which destroyed only bacteria and no other part of the organism.

While working on his monograph on the organism's need for oxygen (*Das Sauerstoff Bedürfnis des Organismus*) in 1883, Ehrlich took one of his rare evenings off to visit friends in Berlin; another guest was their pretty young relative, Hedwig Pinkus, daughter of a wealthy Silesian textile manufacturer. The 18-year-old blonde was not impressed with Ehrlich, whose fingers were covered with the stains of his laboratory work. But when the young scientist called on her he charmed her with his earnestness and enthusiasm, although on his first visit he absentmindedly brought along three top hats. The next year they were married, and she turned out to be the ideal wife for a genius: she protected him from worry about everyday matters, tolerated his eccentricities, let him pour out his heart for hours over his laboratory problems (about which she understood little), provided him with extra funds for his experiments, made his home a blissful haven.*

When the kindly Dr. von Frerichs died, his successor at the Charité hospital interfered with Ehrlich's experiments and insisted that he limit himself to clinical medicine. Ehrlich showed signs of strain, developed pulmonary tuberculosis. He resigned from the hospital and went to Egypt for two years

*They had two daughters.

with his bride; in the warm, dry climate he completely recovered.

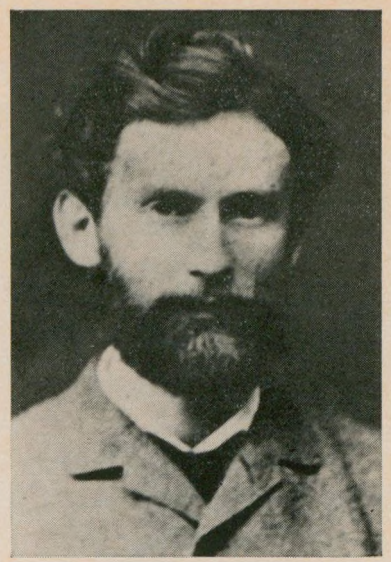
Wrote an intimate friend about this period: "Ehrlich's mind could not bear any bonds. Just as a highly-strung racehorse would end by quivering helplessly in the yoke, breaking down as a result of nervous excitement, so Ehrlich's body would pine away when his spirit was fettered. . . . His illness was called tuberculosis of the lungs, and he had the clinical symptoms of that disease. But what he was suffering from mostly was constraint. The easily cured tuberculosis never troubled him again, once he had recovered his strength."

Immunology. Back in Berlin in 1889, Ehrlich was as dynamic and enthusiastic as before; he gave up medical practice and set up a small private laboratory at his own expense. He threw himself into the problems of immunity, then of consuming interest in German medicine. Emil von Behring and Shibasaburo Kitasato had discovered the concept of antitoxins, but it was still unclear how they functioned.

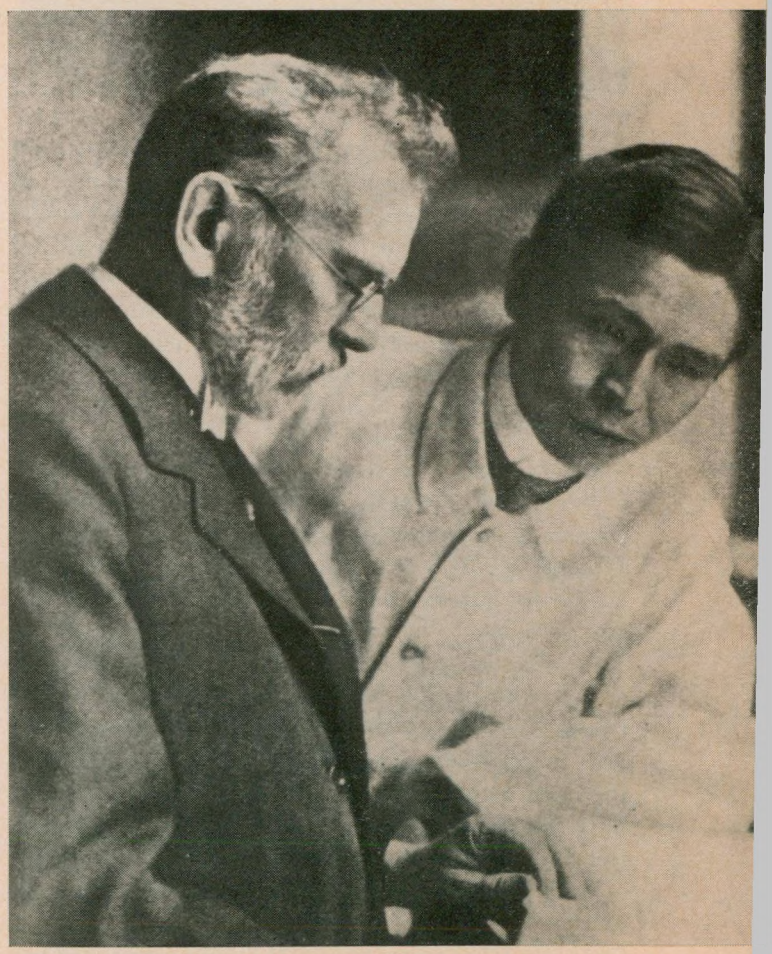
Koch invited Ehrlich to participate in the research at the newly created Institute for Infectious Diseases, where the chief concern was the diphtheria antitoxin: it had failed so often that even Von Behring feared that it would have to be discarded in practical therapy.

After ten years of intensive work, Ehrlich raised the potency of the antitoxic serum and devised a method for standardizing the doses to the point where it became a trustworthy remedy; his techniques are still in use today. In the course of these studies, he worked out the concept of the minimum lethal dose for measuring toxicity in other drugs, also still in use; and the chemotherapeutic index, the ratio between poisons and curative doses, the basis on which modern serotherapy stands. He also established the difference between active and passive immunity, and disproved the then popular belief that the immunity passed on by mother to infant was hereditary; he demonstrated with mice that immunity was transferred from the blood of the mother through the placenta and later through the milk while nursing.

Ehrlich's studies culminated in a startling theory of immunity (the side-chain theory) by which the living organism shields itself from a second infection by producing substances that selectively combine with and neutralize the toxin which they have to counteract. His hypothesis was that the molecule of living protoplasm contains a central stable nucleus and unstable peripheral side-chains which neutralize the toxins when they are introduced into the circulatory system. This theory revolutionized research into immunity and allergy, and is still used as a starting point for many investigations. In 1908 Ehrlich shared with Elie Metchnikoff the Nobel



Paul Ehrlich as a young man, left, and Hedwig Pinkus, at about the time she married him. Although she was not gifted scientifically, Mrs. Ehrlich proved to be an ideal wife. She shielded him from domestic details, heard his problems, provided funds for experiments.



Dr. Ehrlich and Dr. Sakachiro Hata, a pupil of Dr. Shibasaburo Kitasato. Dr. Hata collaborated with Dr. Ehrlich in discovering the therapeutic value of salvarsan.

Dr. Ehrlich in his office at the Institute for Experimental Therapy at Frankfurt, about 1910, two years after he won the Nobel Prize. He was also director of the privately endowed George Speyer House for Chemotherapy.

Prize for Medicine in recognition of his work in immunity.

Chemotherapy. When Ehrlich was still a young physician experimenting with dyes he dreamed of "finding magic bullets which, like those of the ancient fable, cannot miss their mark, and will destroy only the pathogenic agents against which they are aimed." As early as 1891 he began testing methylene blue as a possible remedy for malaria, but he dropped the investigation partly for lack of experimental material and money, partly because of his greater interest in antitoxins.

Twenty-two years later, now famous and the head of two great research institutes in Frankfurt, the government-sponsored Institute for Experimental Therapy and the privately endowed George Speyer House for Chemotherapy, Ehrlich returned to his earlier quest.

In a French scientific journal, he read of the discovery that *mal de caderas*, a paralytic disease of horses (and dogs) was caused by the large protozoan parasite *Trypanosoma equinum*, and that all the mice inoculated with this organism died in four days. Ehrlich decided that here was a perfect subject for experiments on disease-fighting chemicals.

With Kitasato's pupil, Dr. Kikoshi Shiga (discoverer of the germ responsible for bacillary dysentery), he tried more than 500 known dyes, but not one saved a single mouse from the trypanosome. Then Ehrlich and Shiga tested the new benzopurpurine dyes, developed hundreds of variations; finally one, trypan red, worked: one dose cured the infected mice, but it had no effect on other animals.

Shortly thereafter Ehrlich read in a British journal that atoxyl, an arsenic compound, offered some promise in experimental trypanosomiasis. He found that despite its name, atoxyl was toxic, and that when modified it had dangerous side effects. During several years he and his assistants turned out 605 variations of the drug in the hope that it would prove to be both safe and potent. Success came in 1907 with the 606th derivative, diamino dihydro arsenobenzoene dihydrochloride (arsphenamine) synthesized by Ehrlich with the collaboration of Alfred Bertheim and Ludwig Benda: it cured the *mal de caderas.*

While these experiments were going on, Kitasato sent Ehrlich another one of his brilliant young pupils, Dr. Sakachiro Hata; shortly after the syphilis spirochete had been discovered in 1905, Hata had produced the disease experimentally in rabbits. Since certain arsenic drugs had been known for several years to have some effect on syphilis, Ehrlich asked Hata to test 606 in the disease. The tests were an unquestioned success: salvarsan (as Ehrlich then named the drug) cured rabbits of syphilis. Experiments in local hospitals showed that it was a powerful remedy for syphilis in man as well.

Ehrlich first announced the development of salvarsan at the Congress for Internal Medicine at Wiesbaden on April 19, 1910, and became a hero.

(Continued on page 259)

Swamped with requests for the drug, in one year he provided (without charge) some 65,000 doses. It was soon in use in practically every country of the globe, although neither salvarsan, nor an improved version, neosalvarsan (compound 914) also devised by Ehrlich, proved entirely safe in hands less skilled than his. Physicians who did not follow every detail of his meticulous instructions often lost their patients; the disasters received wide publicity and Ehrlich was blamed.

Last Years. To the end of his life Ehrlich was plagued with worries about treatments with the new drugs. He followed the progress of thousands of patients who were given injections; when relapses occurred, Ehrlich asked for every detail of the treatment; he worked night and day to improve both the old and the new forms of salvarsan.

Grave disappointment to him was that salvarsan did not become the *therapia sterilisans magna* for syphilis, by which one injection would cure the disease. But Ehrlich lived to see it cure relapsing fever, yaws, certain forms of angina, Aleppo boil.

For decades Ehrlich neglected his health, ate irregularly and smoked about 25 cigars a day. The result was anorexia and the deterioration of his vascular system, neither of which kept him from working more than the limit of his powers. When his physicians put him on a strict diet of three meals a day and prohibited him from smoking, he became depressed and ill.

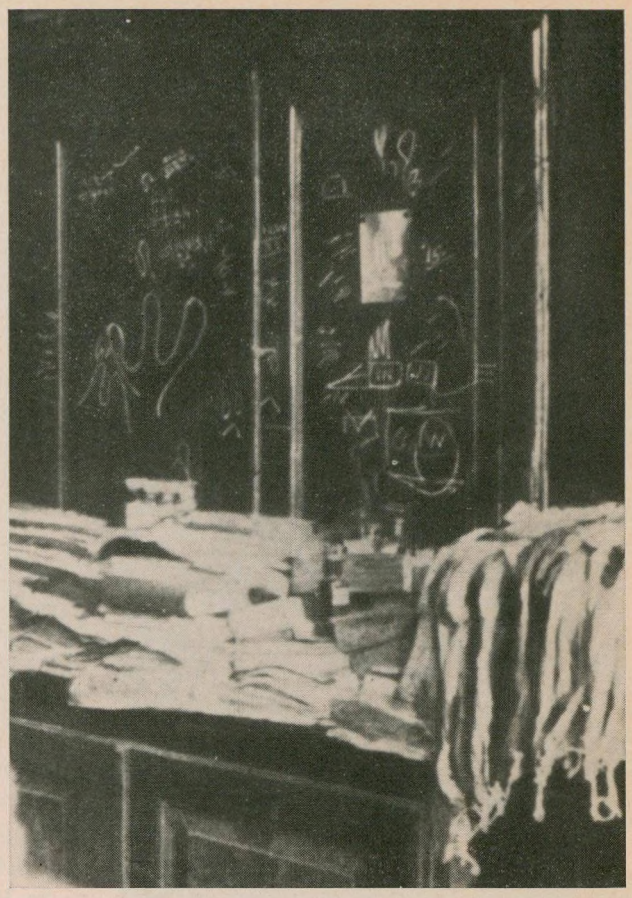
On Christmas Day, 1914, he suffered a slight stroke from which he recovered so quickly that he refused to take it seriously. But six months later he was so weak he could only work a few hours a day. Discouraged, he went to the sanatorium of a friend at Bad Homburg, but within a week (on August 20, 1915) a second stroke ended his life at 61; his wife, one of his daughters and his beloved grandchildren were with him when he died.

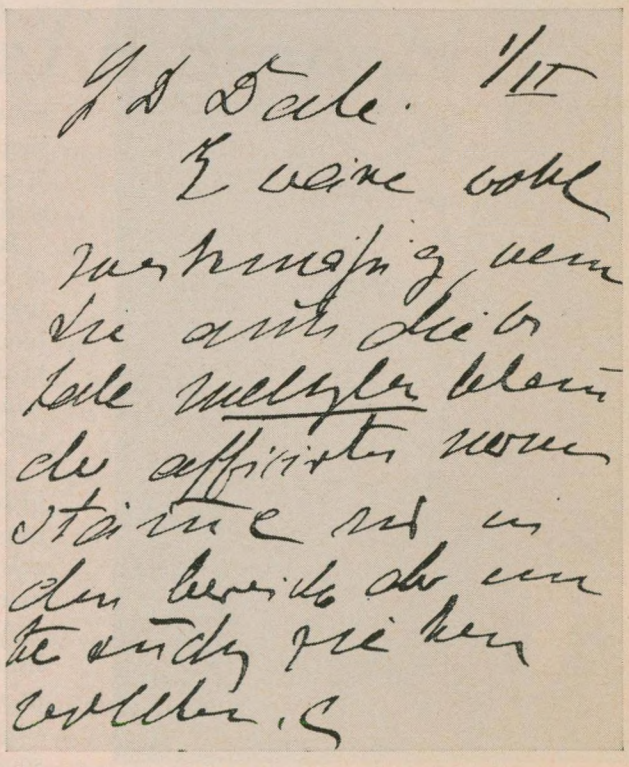
The Scientist. During 40 years in medical research, Ehrlich was uncompromisingly dedicated to his work; although he loved his family, he saw them little. He called himself a "monoman," a man with a single purpose, scientific advancement.

With rare exceptions Ehrlich worked seven days a week; he rose at eight, took his breakfast alone in his study. While he ate he worked, read his mail, wrote out instructions for his assistants. Notes were on red, pink, yellow or blue pads, a different color for each department at the institutes.

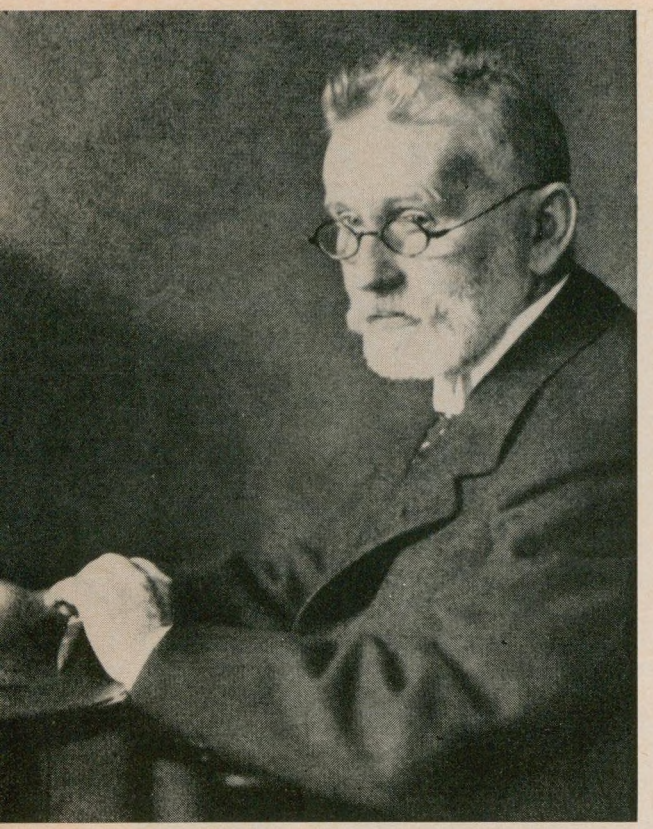
From about ten until one he made the rounds of the laboratories, dictated to his secretary, worked on his own experiments, read scientific journals and conversed with visiting scientists until about six. He usually ate nothing until dinner, was sustained by many huge cigars and glasses of mineral water.

After dinner he would ask his wife to play Vienna





At top, a blackboard in Dr. Ehrlich's laboratory and a cupboard piled high with volumes of his notes. Above, a handwritten note that reads: "It would perhaps be profitable if you would also take the vital dyeing with methylene blue into the field of your investigations."



At top, Dr. Ehrlich as he appeared in his last years. Above, film actor Edward G. Robinson in makeup as Dr. Ehrlich in the 1940 film Dr. Ehrlich's Magic Bullet, *a cinematic account of the scientist's great achievements.*

waltzes for him on the piano while he made notes for the next day; after she retired, he continued working until after midnight.

A small, thin, absentminded man, Ehrlich often paced the floor for hours talking to himself and shouting at imaginary opponents. His only diversion was a detective story magazine which he read every week. He scribbled formulas everywhere he went; on the menus of beer halls where he sometimes supped with his collaborators, on the walls of his bedroom, on the dining room tablecloth. Once while attempting to explain the side-chain theory to a colleague in a railway compartment, he drew diagrams on the sole of his shoe.

Although painfully shy in society, Ehrlich fought vigorously for his radical ideas. He was a familiar figure in cafés and scientific meetings, rising and waving his cigar excitedly as he sought to drive home a point. Ehrlich's own laboratory was a wild clutter of test tubes, flasks, books, manuscripts, the arrangement of which only he understood; yet his method of work was surprisingly simple: using only a few test tubes and a Bunsen burner, he experimented until he found a chemical reaction which seemed interesting; he described it to an assistant, suggested a course of action, and set him to work.

Ehrlich also lectured at medical meetings abroad. In 1904 he visited the United States, spoke in New York, Baltimore, Washington, Chicago.

Once he described his scientific method as "trying not to give directions to nature but only to discover her immutable laws." He added with a smile that scientific achievement depends on four "G's": *"Geld, Geduld, Geschick, Glück."* (money, patience, skill, luck.)

Influence. Ehrlich was a towering figure in an age of scientific giants: he revolutionized biology, histology, immunology, bacteriology, pathology and biochemistry; he coined the term "chemotherapy" to distinguish it from the pharmacology of his day which only analyzed the effects of drugs on patients without seeking specific remedies.

Noted by Henry Sigerist and other great medical historians is that in his constant search for specific remedies for specific illnesses, Ehrlich revived Paracelsus' philosophic spirit in an age of scientific materialism.

Although he hated to write monographs, he published 232 papers and books, most of them dictated in one mighty effort, without a rough draft; he inspired publication of over 400 articles by associates. Many of his pupils, notably Professor Gerhard Domagk, discoverer of the sulfonamides, used his methods to make further scientific advances.

Summing Up. By the New York *Times* at his death: "He opened new doors to the unknown and the whole world is his debtor."